

5-NITROBENZOFURANS

5

BACKGROUND OF THE INVENTION

Field of the Invention: The present invention relates to 5-nitrobenzofurans, to a process for preparing 5-nitrobenzofurans, as well as to 5-nitro-2,3-dihydrobenzofuran-3-ols, to a process for the preparation thereof and to their intermediates.

Brief Description of the Invention: Benzofurans have acquired industrial importance in particular as intermediates for preparing medicaments. The benzofuran structure is found for example in anti-arrhythmic active ingredients such as, for example, amiodarone and bufuralol.

2-(n-butyl)-5-nitrobenzofuran is used as intermediate in the preparation of dronedarone (N-[2-(n-butyl)-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide), which likewise has anti-arrhythmic activity.

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EP-A 0 471 609 describes a process for preparing 2-(n-butyl)-5-nitrobenzofuran which starts from 2-hydroxy-5-nitrobenzyl bromide. This involves reaction with triphenylphosphane initially to prepare 2-hydroxy-5-nitrobenzyltriphenylphosphonium bromide, which is acylated with pentanoyl chloride in the presence of an amine base and subsequently cyclized to 2-(n-butyl)-5-nitrobenzofuran. The disadvantages of this process are the costly precursor 2-hydroxy-5-nitrobenzyl bromide, the low yield and the large amounts of waste, in particular of triphenylphosphane oxide.

WO-A 01/28974 and WO-A 01/29019 disclose processes for preparing 5-nitrobenzofurans, starting from salicylaldehyde, and proceeding in a four-stage synthesis via 2-(2-formyl-4-nitrophenoxy) carboxylic acids as intermediates. The

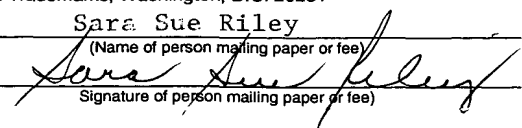
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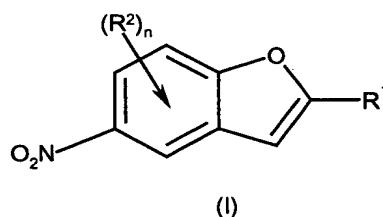
disadvantages of this process are the cost of salicylaldehyde, and the fact that the oxidation-sensitive aldehyde functionality is present in all intermediates.

In a further process disclosed in EP-A 1 116 719, 5-nitro-2(3H)-benzofuranone is reacted in the presence of pentanoic acid and pentanoic anhydride to give 3-(1-hydroxypentylidene)-5-nitro-2(3H)-benzofuranone which reacts under acidic conditions to give 2-(n-butyl)-5-nitrobenzofuran. The disadvantage of this process is that 5-nitro-2(3H)-benzofuranone is used as precursor, which makes industrial application uneconomic.

There was thus a continuing need to develop an efficient and widely applicable process for preparing 5-nitrobenzofuranones which both starts from low-cost, easily obtainable precursors and can easily be implemented industrially.

SUMMARY OF THE INVENTION

A process for preparing compounds of the formula (I) has now been found



in which

R^1 is hydrogen or C_1 - C_{12} -alkyl, and

R^2 are in each case independently of one another: fluorine, chlorine, bromine, iodine, C_1 - C_{12} -alkyl, C_1 - C_{12} -alkoxy, hydroxyl, NR^3R^4 or $CONR^3R^4$, where R^3 and R^4 are each, independently of one another, hydrogen or C_1 - C_{12} -alkyl, or NR^3R^4 as a whole is a cyclic amino radical having 4 to 12 carbon

atoms, $\text{COO}-(\text{C}_1\text{-C}_{12}\text{-alkyl})$, $-\text{COO}(\text{C}_4\text{-C}_{24}\text{-aryl})$, $-\text{COO}(\text{C}_5\text{-C}_{25}\text{-arylalkyl})$,
 $\text{CO}(\text{C}_1\text{-C}_{12}\text{-alkyl})$, $\text{CO}(\text{C}_4\text{-C}_{24}\text{-aryl})$ or $\text{C}_1\text{-C}_{12}\text{-fluoroalkyl}$ and

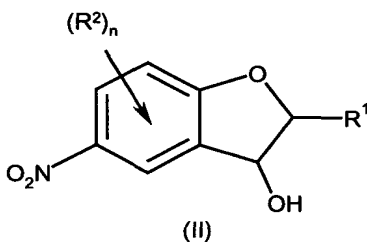
n is zero, one, two or three, or

5 in the case where n is two or three it is possible for two adjacent R^2
substituents to be part of a fused ring system which in turn may optionally
be substituted by the radicals mentioned above for R^2 ,

which is characterized in that

10

compounds of the formula (II)



15 in which

R^1 , R^2 and n have the meaning under formula (I),

are converted by dehydration into compounds of the formula (I).

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For the purposes of the invention it is possible for all the radical definitions,
parameters and explanations which are general or specified in preferred ranges and
are given above and detailed below to be combined with one another in any way,
that is to say also between the respective ranges and preferred ranges.

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DETAILED DESCRIPTION OF THE INVENTION

Alkyl or alkoxy is in each case independently a straight-chain, cyclic, branched or unbranched alkyl or alkoxy radical. The same applies to the nonaromatic part of an arylalkyl radical.

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C₁-C₄-Alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and tert-butyl, C₁-C₈-alkyl is additionally, for example, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 1-ethylpropyl, cyclohexyl, cyclopentyl, n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1,2-dimethylpropyl, 1-methyl-
10 pentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1-ethyl-2-methylpropyl, n-heptyl and n-octyl, and C₁-C₁₂-alkyl is furthermore, for
15 example, adamantyl, the isomeric menthlys, n-nonyl, n-decyl and n-dodecyl.

C₁-C₄-Alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy and tert-butoxy, C₁-C₈-alkoxy is additionally n-pentoxo, 1-methyl-
20 butoxy, 2-methylbutoxy, 3-methylbutoxy, neopentoxo, 1-ethylpropoxo, cyclohexoxy, cyclopentoxo, n-hexoxy and n-octoxy, and C₁-C₁₂-alkoxy is furthermore, for example, adamantoxo, the isomeric menthoxy radicals, n-decoxy and n-dodecoxy.

Fluoroalkyl is in each case independently a straight-chain, cyclic, branched or
25 unbranched alkyl radical which is substituted once, more than once or completely by fluorine atoms.

C₁-C₁₂-Fluoroalkyl is, for example, trifluoromethyl, 2,2,2-trifluoroethyl, penta-
fluoroethyl, nonafluorobutyl, heptafluoroisopropyl, perfluorooctyl and per-
30 fluorododecyl.

Aryl is in each case independently a heteroaromatic radical having 4 to 24 carbon atoms in the framework, in which zero, one, two or three carbon atoms in the framework of each ring, but at least one carbon atom in the framework of the whole molecule, can be replaced by hetero atoms selected from the group of nitrogen, sulphur or oxygen, but is preferably a carbocyclic aromatic radical having 6 to 24 carbon atoms in the framework.

Examples of carbocyclic aromatic radicals having 6 to 24 carbon atoms in the framework are phenyl, naphthyl, phenanthrenyl, anthracenyl or fluorenyl, and heteroaromatic radicals having 4 to 24 carbon atoms in the framework in which zero, one, two or three carbon atoms in the framework of each ring, but at least one carbon atom in the framework of the whole molecule, can be replaced by heteroatoms selected from the group of nitrogen, sulphur or oxygen are, for example, pyridinyl, oxazolyl, benzofuranyl, dibenzofuranyl or quinolinyl.

The carbocyclic aromatic radical or heteroaromatic radical may additionally be substituted by up to five identical or different substituents per ring, which are selected from the group of chlorine, fluorine, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, di(C₁-C₈-alkyl)amino, COO(C₁-C₈-alkyl), CON(C₁-C₈-alkyl)₂, COO(C₁-C₈-arylalkyl), COO(C₄-C₁₄-aryl), CO(C₁-C₈-alkyl), C₅-C₁₅-arylalkyl or tri(C₁-C₆-alkyl)siloxy.

C₄-C₂₄-Aryl is, for example, and preferably, phenyl, o-, p-, m-tolyl, o-, p-, m-anisyl, o-, p-, m-fluorophenyl, o-, p-, m-chlorophenyl, o-, p-, m-trifluoromethylphenyl, o-, p-, m-nitrophenyl and 2-, 3- and 4-pyridyl.

Arylalkyl is in each case independently a straight-chain, cyclic, branched or unbranched alkyl radical as defined above which can be substituted once, more than once or completely by aryl radicals as defined above.

C₅-C₁₅-Arylalkyl is, for example and preferably, benzyl or (R)- or (S)-1-phenylethyl.

The preferred substitution pattern for compounds of the formulae (I) and (II) is defined below:

R¹ is preferably hydrogen or C₁-C₄-alkyl and particularly preferably n-butyl.

R² is preferably in each case independently: fluorine, chlorine, C₁-C₄-alkyl, C₁-C₄-alkoxy, hydroxyl, COO-(C₁-C₄-alkyl), trifluoromethyl, NR³R⁴ or CONR³R⁴, where R³ and R⁴ are each independently of one another hydrogen or C₁-C₄-alkyl, or NR³R⁴ as a whole is pyrrolidinyl or piperidinyl.

n is preferably zero or one, and more preferably zero.

The very particularly preferred compound of the formula (I) is 2-(n-butyl)-5-nitro-benzofuran.

Apart from 2-(n-butyl)-5-nitrobenzofuran, the compounds of the formula (I) are likewise included by the invention and represent starting materials for the development of new active ingredients for the treatment of cardiac arrhythmias.

The compounds of the formula (II) are also furthermore included by the invention. The very particularly preferred compound of the formula (II) is 2-(n-butyl)-5-nitro-2,3-dihydrobenzofuran-3-ol. Moreover, in the case of the compounds of the formula (II) where R¹ is not hydrogen, the (2R,3R); (2S,3S); (2S,3R) and (2R,3S) isomers each in pure form, and any mixtures of the isomers, are encompassed by the invention.

Particularly suitable dehydrating reagents, which may be employed in catalytic amounts where appropriate, for the purposes of the invention are: protic acids such as H_2SO_4 or H_3PO_4 or bisulphates such as KHSO_4 , hydroxides such as NaOH and KOH , P_2O_5 , I_2 , and salts of zinc and copper such as, in particular, CuSO_4 and ZnCl_2 . Protic acids are particularly preferred for the process of the invention. H_2SO_4 is very particularly preferred for the process of the invention.

The dehydration can be carried out in an organic solvent. Organic solvents preferably used are polar, protic and aprotic solvents. Polar solvents mean those having a dielectric constant at 25°C of 5 or more. Organic solvents particularly preferred for the process of the invention are aliphatic C_1 - C_6 -alcohols. Ethanol is very particularly preferred for the process of the invention.

The dehydration can be carried out for example at temperatures from -20 to 150°C , preferably at 20 to 150°C , particularly preferably at 50 to 100°C and very particularly preferably at 70 to 78°C .

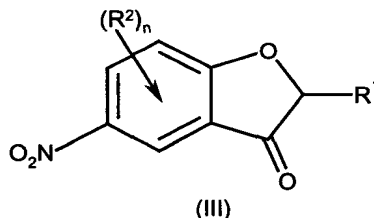
The reaction may take for example from 0.5 to 20 hours, preferably 0.5 to 8 hours and particularly preferably from 4 to 5 hours.

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The pressure during the reaction is not critical and can be, for example, 0.5 to 100 bar, preferably 0.8 to 10 bar. Ambient pressure is particularly preferred.

The compounds of the formula (II) can be obtained in a particularly advantageous manner by reducing compounds of the formula (III)

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in which

R^1 , R^2 and n have the meanings specified under formula (I), including the preferred ranges.

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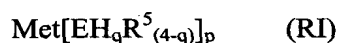
Compounds of the formula (III) encompassed by the invention are those in which R^2 and n have the meanings specified under formula (I), including the preferred ranges, and R^1 is *n*-butyl. A particularly preferred compound of the formula (III) is 2-(*n*-butyl)-5-nitro-3(2H)-benzofuranone.

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The compounds of the formula (III) can be reduced for example by transfer hydrogenation or by means of aluminium-hydrogen or boron-hydrogen compounds. The reduction is preferably effected by aluminium-hydrogen or boron-hydrogen compounds, particularly preferably by compounds of the formula

15

(RI)



in which

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Met is a monovalent or divalent metal such as, preferably, zinc, lithium, sodium or potassium, and

E is aluminium or boron and

25

R^5 is C_1 - C_8 -alkyl, and

q is 1,2,3 or 4, preferably 4 or 1 and

30

p is the valency of Met,

or by compounds of the formula (RII)



5 in which

R^5 has the meaning specified under formula (RI), and

r is one, two or three.

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Very particularly preferred compounds of the formulae (RI) and (RII) are LiBH_4 , NaBH_4 , $\text{Zn}(\text{BH}_4)_2$, LiAlH_4 , $\text{Li}[\text{BHEthyl}_3]$ and $\text{Li}[\text{AlH}(\text{sec-butyl})_3]$, with NaBH_4 being even further preferred.

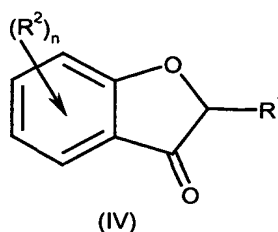
15 The amount of the aluminium-hydrogen or boron-hydrogen compounds is preferably chosen so that the molar ratio of hydrogen in the aluminium-hydrogen or boron-hydrogen compounds and the substrate is from 0.5 to 10, preferably 0.95 to 5 and particularly preferably 1.0 to 1.2. Larger ratios are possible but uneconomic.

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Depending on the reagent employed, it is possible to employ polar solvents as solvents. The use of alkali metal boranates in aliphatic C_1 - C_6 -alcohols or ethers such as, in particular, 1,4-dioxane is preferred for the process of the invention. The reduction is very particularly preferably carried out with sodium borohydride in
25 ethanol.

The reaction can be carried out for example at temperatures from -78 to 100°C , preferably 0 to 100°C and particularly preferably 60 to 78°C .

The compounds of the formula (III) can be obtained in a particularly advantageous manner by nitration of compounds of the formula (IV)



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in which R^1 , R^2 and n have the meanings specified under formula (I), including the preferred ranges.

The reagents advantageously employed for the nitration are those able to generate
10 nitrile cations (NO_2^+). Nitric acid is preferred for example, preferably with a
content of from 60 to 100% by weight based on HNO_3 . The use of nitric acid,
where appropriate as a mixture with sulphuric acid with a content of from 50 to
160% by weight based on H_2SO_4 and/or phosphoric acid with a content of from 70
to 160% by weight based on H_3PO_4 , is likewise preferred. The use of nitrogen
15 oxides such as NO_2 , N_2O_3 , N_2O_4 , N_2O_5 or of NO is additionally preferred, where
appropriate in the presence of an oxidizing agent. Preference is likewise given to
nitration with nitrous acid HNO_2 or a salt of nitrous acid such as, in particular,
 NaNO_2 , preferably in the presence of an oxidizing agent, or with ionic nitrile
compounds such as, for example, $\text{NO}_2^+\text{BF}_4^-$. Alkyl nitrites of the general formula
20 $\text{R}^6\text{-ONO}$, where R^6 is $\text{C}_1\text{-C}_{12}$ -alkyl, are further preferably to be employed for the
nitration.

The amount of nitration reagent employed is advantageously chosen so that the
molar ratio of theoretically nitrating agent to compound of the formula (IV) is
25 from 0.9 to 2, preferably 1.0 to 1.5 and particularly preferably 1.0 to 1.2.

A mixture of nitric acid with a content of from 60 to 100% by weight based on HNO_3 and sulphuric acid with a content of from 90 to 100% by weight based on H_2SO_4 is particularly preferably employed for the nitration.

- 5 Likewise particularly preferred for the nitration is nitric acid with a content of from 95 to 100% by weight.

In a preferred embodiment, the molar ratio of compound of the formula (IV) and nitric acid is between 0.9 and 1, particularly preferably between 0.95 and 1.05.

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- The nitration can be carried out for example with or without organic solvent, the organic solvent necessarily being inert under reaction conditions. Representatives of such organic solvents which may be particularly mentioned are halogenated aliphatic hydrocarbons such as, in particular, chlorinated aliphatic hydrocarbons
15 such as, for example, dichloromethane, 1,2-dichloroethane, tetrachloromethane and hexachloroethane. Dichloromethane is preferred for the nitration of compounds of the formula (IV).

However, the nitration is preferably carried out without organic solvent.

- 20 The amount concentration of the compound of the formula (IV) in the reaction medium can be, for example, from 0.2 to 3 mol/l, and from 0.3 to 1.6 mol/l is preferred.

- The nitration can be carried out for example in a temperature range from -10 to
25 50°C, preferably between -10 and 20°C, particularly preferably between -5 to 10°C.

- The process of the invention can be carried out under an inert gas atmosphere at atmospheric pressure, with the procedure possibly being for example as follows:
30 for example it is possible to introduce the sulphuric acid first and then to meter in

the compound of the formula (IV) and the nitric acid or a mixture of nitric acid and sulfuric acid. A further possibility is also for the nitric acid and the sulphuric acid to be introduced first and then the compound of the formula (IV) to be added, preferably in portions.

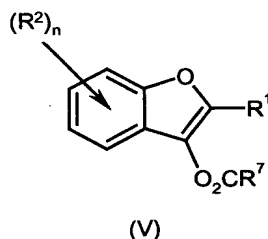
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The reaction may take, depending on the amount employed, for example and preferably from 0.1 to 10 hours.

The product can be isolated by using the techniques which are customary in nitration reactions and are known to the skilled person. It is preferred for the process of the invention to transfer the reaction mixture to ice or ice-water and then filter or extract.

The compounds of the formula (IV) can be obtained in a preferred manner by hydrolysing compounds of the formula (V)

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in which

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R^1 , R^2 and n have the meaning specified under formula (I), including the preferred ranges, and

R^7 is C_1 - C_{12} -alkyl, C_5 - C_{25} -arylalkyl, C_4 - C_{24} -aryl or C_1 - C_{12} -fluoroalkyl,

25

R^7 is preferably C_1 - C_4 -alkyl and particularly preferably methyl.

The hydrolysis can in this case be carried out with acids, bases, metal ions, enzymes or nucleophiles, where appropriate in catalytic amounts, and where appropriate in the presence of an organic solvent.

- 5 Preferably employed are bases such as, for example, aqueous amines such as, in particular, aqueous ammonia, hydroxides or carbonates such as, in particular, NaOH and KOH or acids such as, for example, aqueous hydrochloric acid, sulphuric acid, phosphoric acid, bisulphates, carboxylic acids such as, for example, formic acid or acetic acid, and sulphonic acids such as, for example, methanesulphonic acid or *para*-toluenesulfonic acid in various concentrations.
- 10

Acids are particularly preferably employed, very particularly preferably hydrochloric acid, sulphuric acid, or phosphoric acid, with 6N hydrochloric acid being even further preferred.

15

The acid is in this case preferably employed in amounts such that the molar ratio of compounds of the formula (V) to acid is from 1:1 to 1:100, preferably 1:1.1 to 1:10 and particularly preferably 1:5 to 1:6.

- 20 It is possible in a preferred embodiment to employ an organic solvent to improve the solubility of the compounds of the formula (V). Vigorous stirring and the use of ultrasound or of phase-transfer catalysts is also possible in addition. Preferred organic solvents are aliphatic C₁-C₆-alcohols or cyclic ethers. Ethanol is particularly preferably employed.

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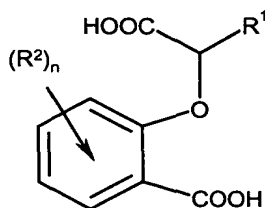
The reaction can be carried out at temperatures from 25 to 200°C, preferably at 60 to 100°C, particularly preferably at 70 to 78°C.

- The reaction may last for example from 0.5 to 24 hours, and 1 to 6 hours are preferred.
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The compounds of the formula (V) encompassed by the invention are those in which R^2 and n have the meanings specified under formula (I), including the preferred ranges, R^7 has the abovementioned meaning, including the preferred ranges thereof, and R^1 is n-butyl. A particularly preferred compound of the

5 formula (V) is 3-acetoxy-2-(n-butyl)benzofuran.

The compounds of the formula (V) can be obtained in a particularly advantageous manner by cyclizing decarboxylation of compounds of the formula (VI)



(VI)

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in which R^1 , R^2 and n have the meanings specified under formula (I), including the preferred ranges,

15 in the presence of at least one compound of the formula (RIII)



in which

20 R^7 has the meaning specified under formula (V), including the preferred ranges, and

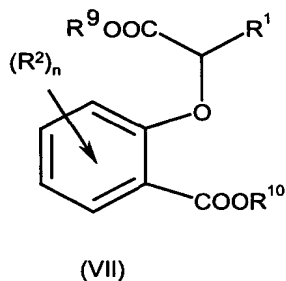
R^8 is $-O_2CR^7$, hydroxyl or OM, where M is an alkaline earth metal or alkali metal.

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The reaction is preferably carried out in the presence of a mixture of compounds of the formula (RIII), employing in each case an anhydride, preferably a homoanhydride $(R^7CO)_2O$, an alkali metal salt and a free acid. The R^7 radicals in the said compounds are preferably identical in each case. It is particularly preferred to employ mixtures of sodium acetate, acetic acid and acetic anhydride. The ratio of the amount of substances in this case is preferably (0.8 to 1.5):(2 to 4):(3 to 8), particularly preferably about 1:3:5.

The reaction temperature can be for example from 20 to 150°C, preferably 60 to 150°C and particularly preferably 120 to 140°C.

The compounds of the formula (VI) can be obtained in a preferred manner by hydrolysing compounds of the formula (VII)



in which

R^1 , R^2 and n have the meanings specified under formula (I), including the preferred ranges, and

R^9 and R^{10} are each independently of one another C_1 - C_{12} -alkyl, C_5 - C_{25} -arylalkyl or C_4 - C_{24} -aryl, and not more than one R^9 or R^{10} radical can be hydrogen.

R⁹ and R¹⁰ are preferably each independently of one another C₁-C₄-alkyl, particularly preferably each independently of one another methyl or ethyl and very particularly preferably each identically methyl or ethyl.

- 5 The hydrolysis can in this case be carried out with acids, bases, metal ions, enzymes or nucleophiles, where appropriate in catalytic amounts, and where appropriate in the presence of an organic solvent.

- Bases such as, for example, aqueous amines such as, in particular, aqueous ammonia, hydroxides such as, in particular, LiOH, NaOH, KOH and Ca(OH)₂, carbonates such as Na₂CO₃, K₂CO₃ or CaCO₃ or aqueous acids such as, for example, hydrochloric acid, sulphuric acid, phosphoric acid, bisulphates, carboxylic acids such as, for example, formic acid or acetic acid, and sulphonic acids such as, for example, methanesulphonic acid or *para*-toluenesulfonic acid
15 are preferably employed.

- In a preferred embodiment, the hydrolysis is carried out in the presence of bases, with the use of LiOH, NaOH, KOH or Ca(OH)₂ being preferred. It is particularly preferred to use sodium hydroxide solution with a content of from 5 to 25% by
20 weight. It is furthermore possible in a preferred embodiment to employ an organic solvent to improve the solubility of the compounds of the formula (VII).

- For efficient hydrolysis of the ester groups, the base is preferably employed in amounts such that the molar ratio of base to compounds of the formula (VII) is
25 from 1.5:1 to 20:1, preferably 2:1 to 7:1 and particularly preferably 3:1 to 5:1.

An organic solvent can be employed to improve the solubility of the substrate. Vigorous stirring and the use of ultrasound or of phase-transfer catalysts is additionally possible. The organic solvents preferably used for the process of the

invention are aliphatic C₁-C₆-alcohols or cyclic ethers. Methanol or ethanol is particularly preferably employed.

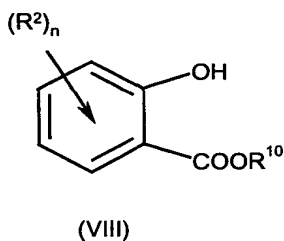
The reaction can be carried out at temperatures from 20 to 200°C, preferably at 40 to 75°C and particularly preferably at 40 to 60°C.

Compounds of the formula (VII) encompassed by the invention are those in which R² and n have the meanings specified under formula (I), including the preferred ranges, R⁹ and R¹⁰ then have the abovementioned meaning, including the preferred ranges thereof, and R¹ is n-butyl. Compounds of the formula (VII) which may be mentioned are:

methyl 2-(1-methoxycarbonylpentoxy)benzoate, ethyl 2-(1-methoxycarbonylpentoxy)benzoate, ethyl 2-(1-ethoxycarbonylpentoxy)benzoate and methyl 2-(1-ethoxycarbonylpentoxy)benzoate, 2-(1-methoxycarbonylpentoxy)benzoic acid, 2-(1-ethoxycarbonylpentoxy)benzoic acid, ethyl 2-(1-carboxypentoxy)benzoate and methyl 2-(1-carboxypentoxy)benzoate, and methyl 2-(1-methoxycarbonylhexoxy)benzoate, ethyl 2-(1-methoxycarbonylhexoxy)benzoate, ethyl 2-(1-ethoxycarbonylhexoxy)benzoate and methyl 2-(1-ethoxycarbonylhexoxy)benzoate, 2-(1-methoxycarbonylhexoxy)benzoic acid, 2-(1-ethoxycarbonylhexoxy)benzoic acid, ethyl 2-(1-carboxyhexoxy)benzoate and methyl 2-(1-carboxyhexoxy)benzoate.

The compounds of the formula (VII) can be obtained in a preferred manner by reacting compounds of the formula (VIII)

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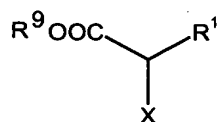
in which

R^2 and n have the meanings specified under formula (I), including the preferred ranges, and

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R^{10} is hydrogen, C_1 - C_{12} -alkyl, C_5 - C_{25} -arylalkyl or C_4 - C_{24} -aryl,

with compounds of the formula (IX)



10

(IX)

in which

15 R^1 has the meanings specified under formula (I), including the preferred ranges,

R^9 is hydrogen, C_1 - C_{12} -alkyl, C_5 - C_{25} -arylalkyl or C_4 - C_{24} -aryl, and

20 X is chlorine, bromine, iodine or $R^{11}SO_3^-$ where R^{11} is C_1 - C_{12} -alkyl, C_4 - C_{24} -aryl, C_5 - C_{25} -arylalkyl or C_1 - C_{12} -fluoroalkyl.

R^{11} is preferably C_1 - C_4 -alkyl or C_4 - C_{24} -aryl, particularly preferably methyl, ethyl, phenyl, o-, m- or p-tolyl or trifluoromethyl.

25 X is preferably chlorine or bromine, particularly preferably bromine.

The compounds of the formula (VIII) which are preferably employed are methyl o-hydroxybenzoate and ethyl o-hydroxybenzoate.

5 The compounds of the formula (IX) which are preferably employed are the methyl or ethyl 2-bromo carboxylates such as, in particular, methyl or ethyl 2-bromohexanoate.

10 The reaction of compounds of the formula (VIII) with compounds of the formula (IX) to give compounds of the formula (VII) is preferably carried out in the presence of base. A possible alternative to this is for the compound of the formula (VIII) first to be converted into the corresponding phenolate and be employed as such in the reaction.

15 The reaction can be carried out in an organic solvent. Reaction in water in the presence of a phase-transfer catalyst is also furthermore possible. Polar protic or aprotic solvents are preferably employed for the process of the invention, such as, for example, ketones such as acetone, amides such as N,N-dimethylformamide or N,N-dimethylacetamide, lactams such as 1,-methyl-2-pyrrolidinone, ethers such as tetrahydrofuran or dioxane, nitriles such as acetonitrile or benzonitrile or alcohols
20 such as methanol or ethanol. Even further preferred for the process of the invention are acetone or acetonitrile.

The reaction can, where appropriate, be carried out under an inert gas atmosphere, for example an argon atmosphere.
25

The bases employed are those which are able at least partly to deprotonate the compounds of the formula (VIII) on the phenol function.

Inorganic bases or organic bases for example can be employed. Organic bases
30 which can preferably be used are tertiary amines such as triethylamine or alkali

metal alcoholates such as sodium methoxide or ethoxide, an inorganic base is for example alkali metal or alkaline earth metal hydroxides, carbonates or bicarbonates. Preferred bases are alkali metal carbonates, especially potassium carbonate or sodium carbonate.

5

The ratio of the amounts of the compounds of the formula (IX) employed and of the compounds of the formula (VIII) is advantageously chosen so that it is between 1.0 and 1.2.

- 10 The ratio of amounts between the base employed and the compound of the formula (VIII) employed is advantageously chosen between 1.0 and 1.5, with a ratio between 1.1 and 1.3 being preferred.

- 15 The reaction can be carried out for example at temperatures from 0 to 150°C, with preferred reaction temperatures being from 50 to 100°C, particularly preferably 70 to 80°C.

- 20 The compounds of the general formula (VI) may, where appropriate, also be prepared directly, without isolating the compounds of the formula (VII), by reacting compounds of the formula (VIII) with compounds of the formula (IX) in a one-pot process with hydrolysis of the ester functions taking place simultaneously.

- 25 An alternative possibility is also to prepare compounds of the formula (VI) by reacting those compounds of the formula (VIII) with those compounds of the formula (IX) in which R⁹ and R¹⁰ are each hydrogen. The amount of base is advantageously increased appropriately in this reaction.

The invention encompasses, besides a process for preparing compounds of the formula (I) from compounds of the formula (II), also processes for preparing

compounds of the formula (I) from compounds of the formula (III), (IV), (V), (VI), (VII), (VIII) and (IX), each of which proceed via the described intermediates. The invention further encompasses processes for preparing compounds of the formula (II) from compounds of the formula (III) and, in each case, from the
5 compounds (IV), (V), (VI), (VII), (VIII) and (IX), each of which proceed via the described intermediates.

The invention further encompasses processes for preparing compounds of the formula (III) from compounds of the formula (IV) and, in each case, from the
10 compounds (V), (VI), (VII), (VIII) and (IX), each of which proceed via the described intermediates.

The compounds of the formulae (I), (II) and (III) prepared according to the invention are particularly suitable for producing medicaments and physiologically
15 active substances and for use in a process for producing medicaments and physiologically active substances.

Preferred medicaments and physiologically active substances in this connection are those employed for treating cardiac arrhythmias. A particularly preferred
20 physiologically active substance is dronedarone.

The invention is distinguished through the fact that 5-nitrobenzofurans, 5-nitro-2,3-dihydrobenzofuran-3-ols and 5-nitro-3(2H)-benzofuranones can be obtained by a highly efficient and economic route, and synthetic processes for a wide
25 spectrum of potential development candidates are disclosed.

The invention is further described by the following illustrative but non-limiting examples.

EXAMPLES**Example 1:** Synthesis of methyl 2-(1-methoxycarbonylpentoxo)benzoate

5 15.2 g of methyl salicylate and 18.0 g of potassium carbonate were introduced into
125 ml of acetonitrile in a 250 ml flask under an argon atmosphere and, at room
temperature, 20.9 g of methyl 2-bromohexanoate were added. The colourless
suspension was heated under reflux with stirring for 16 hours, and the progress of
the reaction was checked by thin-layer chromatography. After cooling to room
10 temperature, the suspension was filtered and the residue was washed with acetone.
Concentration of the filtrate in vacuo resulted in 27.8 g (99% of theory) of methyl
2-(1-methoxycarbonylpentoxo)benzoate as yellow oil.

Example 2: Synthesis of 2-(1-carboxypentoxo)benzoic acid

15 13.0 g of methyl 2-(1-methoxycarbonylpentoxo)benzoate were dissolved in
methanol in a 250 ml flask, and a solution of 9.1 g of sodium hydroxide in 40 ml
of water was added. The reaction mixture was stirred at 40°C for one hour, during
which a precipitate formed. This was dissolved after cooling to room temperature
20 by adding further methanol and sodium hydroxide solution. The reaction mixture
was washed with dichloromethane, and the aqueous phase was subsequently
adjusted to pH 0 with concentrated hydrochloric acid while cooling in ice. A
colourless solid precipitated during this and was filtered off and dried. 10.1 g
(87% of theory) of 2-(1-carboxypentoxo)benzoic acid were obtained in this way.

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Example 3: Synthesis of 3-acetoxy-2-(n-butyl)benzofuran

5.0 g of 2-(1-carboxypentoxo)benzoic acid and 1.6 g of sodium acetate were
introduced into a 25 ml flask, and 3.4 ml of glacial acetic acid and 9.4 ml of acetic
30 anhydride were added. The colourless suspension was heated to reflux for 4 hours.

Cooling, transferring the reaction mixture into ice-water, extracting with dichloromethane, drying the combined organic phases over sodium sulphate and removing the solvent resulted in a yellow oil in which, according to GC, the precursor and the product were present in an approximate ratio (percentage areas) of 50:50.

This oil was again mixed with 1.6 g of sodium acetate, 3.4 ml of glacial acetic acid and 9.4 ml of acetic anhydride and once more heated to reflux for 4 hours. Cooling and the same working up as described above resulted in 4.3 g (92% of theory) of 3-acetoxy-2-(n-butyl)benzofuran as pale yellow oil.

Example 4: Synthesis of 2-(n-butyl)-3(2H)-benzofuranone

4.6 g of 3-acetoxy-2-(n-butyl)benzofuran were dissolved in 20 ml of ethanol in a 100 ml flask, and 20 ml 6N hydrochloric acid were added. The mixture was heated to reflux for 4 hours. After cooling to room temperature, the pH was adjusted to 4 to 6 with sodium hydroxide, and the ethanol was distilled off. This was followed by extraction with dichloromethane. Drying of the combined organic phases over sodium sulphate and removal of the solvent resulted in 2.8 g (76% of theory) of 2-(n-butyl)-3(2H)-benzofuranone as yellow oil.

Example 5: Synthesis of 2-(n-butyl)-5-nitro-3(2H)-benzofuranone

2.9 ml of concentrated sulphuric acid were introduced into a 50 ml flask and cooled to 5°C. Then 1.0 g of 2-(n-butyl)-3(2H)-benzofuranone was slowly added, during which the reaction mixture assumed a brownish colour. It was stirred for 15 minutes. Subsequently, 0.7 g of nitration acid was slowly added dropwise in such a way that the temperature did not rise much above 5°C. The reaction mixture was then poured onto ice, stirred and extracted with dichloromethane. The dichloromethane extracts were washed with water, dried over sodium sulphate and

evaporated to dryness in vacuo. The material (1.0 g) obtained in this way had, according to GC, a content of about 70% (percentage areas) of 2-(n-butyl)-5-nitro-3(2H)-benzofuranone. Further purification is possible by column chromatography (eluent: hexane:ethyl acetate = 10:1).

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^1H NMR (CDCl_3 , 400 MHz): δ = 8.49 (d, J = 2.4 Hz, 1 H, Ar-H), 8.45 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H, Ar-H), 7.17 (d, J = 9.0 Hz, 1 H, Aryl-H), 4.69 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 1 H, O=C-CH), 2.0 – 1.9 ($2 \times$ m, 2 H, CH-CH₂), 1.40 (m, 2 H, CH₂), 1.33 (m, 2 H, CH₂), 0.85 (t, J = 7.2 Hz, 3 H, CH₃).

10

Example 6: Synthesis of 2-(n-butyl)-5-nitro-2,3-dihydrobenzofuran-3-ol

700 mg of 2-(n-butyl)-5-nitro-3(2H)-benzofuranone were introduced into 10 ml of ethanol in a 50 ml flask and cooled to 0°C. A solution of 130 mg of NaBH₄ in 5 ml of ethanol was added dropwise thereto, an intense red coloration immediately appearing. The mixture was allowed to reach room temperature and was then briefly heated to reflux. After cooling to room temperature, the reaction mixture was taken up in water and dichloromethane, the organic phase was separated off, and the aqueous phase was extracted once more with dichloromethane. Drying of the combined organic phases over sodium sulphate, removal of the solvent in vacuo and column chromatography (eluent: hexane:ethyl acetate = 5:1) resulted in 400 mg (57% of theory) of 2-(n-butyl)-5-nitro-2,3-dihydrobenzofuran-3-ol.

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Example 7: Synthesis of 2-(n-butyl)-5-nitrobenzofuran

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300 mg of 2-(n-butyl)-5-nitro-2,3-dihydrobenzofuran-3-ol were introduced into ethanol in a 50 ml flask, and 1 ml of concentrated sulphuric acid was added. The mixture was then heated to reflux for 4 hours. After cooling, 10 ml of water were added, the ethanol was distilled off, and the mixture was extracted with dichloromethane. Washing of the organic phase with sodium bicarbonate solution,

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drying over sodium sulphate and removal of the solvent in vacuo resulted in 220 mg (80% of theory) of 2-(n-butyl)-5-nitrobenzofuran as yellow oil.

5 Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention except as it may be limited by the claims.